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Mesial temporal lobe epilepsy with hippocampal sclerosis: Study of 42 children

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ABSTRACT

Purpose: We present the electroclinical features, treatment, and evolution of patients with mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS).
Material and methods: We analyzed the charts of forty-two patients who met the diagnostic criteria of MTLE-HS. The mean follow-up after seizure onset was 10.5 years.
Results: According to age, we defined three groups. The first group included nine patients that started with seizures before 2 years of age. Motor seizures were the hallmark clinical manifestation. All patients of this group also presented with motor arrest and oro-alimentary automatisms. In three of them, the interictal EEG recordings showed bilateral paroxysms predominantly in anterior regions, in addition to focal abnormalities, and two had an apparently generalized ictal pattern. The second group included 17 patients that started with seizures between 2 and 10 years of age. In this group the automatisms were also oroalimentary, but more complex and the patients had less motor manifestations. The interictal EEG recordings showed temporal abnormalities. The ictal EEG recordings showed lateralized abnormalities with a maximum in the temporal electrodes. The third group included 16 patients that started with seizures between 10 and 16 years of age. The most common clinical manifestation was abdominal aura followed by oroalimentary, gestural, and verbal automatisms. The interictal and ictal EEG recordings showed well-localized abnormalities in temporal lobes. Thirty-eight patients underwent surgical treatment. Thirty-five patients are seizure free.
Conclusion: MTLE-HS represents a well-defined and distinct symptomatic epileptic syndrome. Surgical treatment was successful in most patients.

1. Introduction

Mesial temporal lobe epilepsy (MTLE) syndrome is an entity in which the most predominant seizures are originated in limbic areas of the mesial temporal lobe, particularly in the hippocampus, amygdala, and in the parahippocampal gyrus and its connections. The anatomopathological hallmark is sclerosis of the hippocampus.[1,2]

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is the most common cause of surgical and refractory epilepsy in adulthood.[3] However, the entity has only recently been clearly defined and because only the patients with the medically refractory form referred to epilepsy surgery services are usually identified, epidemiologic data are lacking both for the adult and the pediatric population.

MTLE-HS syndrome is restricted to patients in whom hippocampal atrophy and/or abnormal signal intensity on MRI, anterior temporal interictal epileptiform discharges, and additional evidence of temporal dysfunction on functional images and neuropsychological assessment are demonstrated.[2,4,5]

In the majority of series, MTLE is associated with an "early first insult", such as febrile seizures, a prolonged focal seizure, infection of the central nervous system, or head trauma, among others, most often occurring in the first five years of life. Patients frequently suffer from cognitive impairment – especially related to memory – and behavior disturbances.[2,4,5] Familial forms of MTLE-HS have been recognized, but no causal gene or linkage has been identified so far. MTLE-HS may also occur as a clinical phenotype of febrile seizures plus and epilepsy.[6,7]

After the early insult there is a long "silent period" before the clinical picture is manifested. Seizures initiate with an abdominal aura, a rising epigastric sensation associated with emotional disturbances, such as fear, autonomic symptoms, and, at the end of the aura, oro-alimentary automatisms. There is progressive impairment of consciousness. Dystonic postures may occur. Ictal speech is suggestive of non-dominant hemisphere involvement.

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Seizures last less than 2 min. Seizures are easily controlled at the beginning of the clinical picture and then become refractory. In the refractory cases, surgical resection of the epileptogenic zone is usually successful.[2,4,5]

MTLE-HS seems to occur more rarely in children than in adults and has been less well studied in this population.[8–20] This may be due to the particular electroclinical features of some seizures whose temporal origin is difficult to recognize in young children. The later maturation of the limbic system may also play an important role.[15]

Here, we present the electroclinical features, treatment – mainly the option of surgery – and evolution of patients with MTLE-HS.

2. Material and methods

We analyzed the charts of 42 patients with MTLE-HS seen at our department between June 1989 and May 2008. In the same period, we evaluated 251 patients with refractory focal epilepsies; 33 with other mesial temporal lobe epilepsies, 20 with lateral temporal lobe epilepsy, 10 with both mesial and lateral temporal lobe epilepsy, 70 with frontal lobe epilepsy, 35 with occipital lobe epilepsy, 20 patients with parietal lobe epilepsy, and 21 patients with unclassifiable focal epilepsies. Onset of seizures was between 1 and 16 years of age (mean: 7 years).

The following inclusion criteria were considered[2]:

- Clinical features:
  - Auras, especially epigastric and nonspecific aura (a difficult-to-describe aura including tingling about the midline or entire body, fear and anxiety, emotional auras, an illusion or familiarity and strangeness, including recollection and déjà vu, autonomic-vegetative auras, abdominal pain associated with fear, and olfactory-gustatory auras)
  - Motion arrest
  - Alteration of consciousness (and amnesia)
  - Automatisms
  - Brief seizure duration and seizure spread (positive motor symptoms)
  - Postictal signs and symptoms (cognitive impairment, memory deficit, mood changes, and language deficits)
  - Others (ictal aphasia, ictal anomia)
- EEG features
  - Ictal scalp EEG or depth EEG showing seizure origin from mesial temporal lobe
- MRI imaging with signs compatible with HS
- Neuropsychological evaluation (especially memory)
- Neuropathological findings of HS (surgical cases)

We excluded patients with MTLE secondary to neocortical temporal lobe epilepsy and other etiologies and patients with HS associated with other pathologies, such as tumors and malformations of cortical development. Patients with bilateral temporal lobe epilepsy were also ruled out.

Gender, age at onset of seizures, personal antecedents, history of febrile – or other types of seizures, and family history of febrile seizures and epilepsy were analyzed. Seizure semiology, EEG, video-EEG, depth-electrode recordings (two patients), MRI, neuropsychological tests (Stanford-Binet, Wechsler, and Rey), including intracarotid amobarbital procedure in three patients, AEDs, and developmental and psychomotor evolution were analyzed as well. In the surgical cases, Engel score, type of surgery, and age at surgery were evaluated.

The mean follow-up after seizure onset was 10.5 years (range, 6–17 years).

3. Results

3.1. Number of patients

Twenty-three (54.7%) boys and 19 (45.3%) girls, who met the inclusion criteria of MTLE-HS were studied.

3.2. Age at onset

Age at onset of MTLE-HS was between 1 and 16 years, with a mean age of 8 years and a median age of 7 years. Mean age of the diagnosis was 7 years (range, 1–13 years).

3.3. Personal antecedents and history of febrile seizures

Three patients had had herpes virus encephalitis, three patients skull trauma, and one patient hypovolemic shock. Seventeen patients (44.4%) had had prolonged febrile seizures and six patients (12%) had had prolonged focal seizures. In three of the latter children, the prolonged focal seizures occurred during herpes virus encephalitis, in two in the immediate post-skull trauma period, and in one during hypovolemic shock. The mean and median age at presentation of febrile seizures was 16 and 18 months, respectively (range, 6–50 months).

3.4. Family history of febrile seizures and epilepsy

Five patients (11.9%) had a family history of epilepsy; two patients had a relative with MTLE-HS, two had a relative with focal epilepsy, and one had a relative with generalized epilepsy. Fifteen patients (35.7%) had a family history of febrile seizures.

3.5. Ictal manifestations

Twenty-one patients (50%) had an aura; six patients had an epigastric aura alone, five had an epigastric aura associated with an emotional aura, four had abdominal pain associated with fear, three had olfactory-gustatory auras, one had déjà vu, and two experienced a nonspecific aura. All patients had motor arrest and alteration of consciousness. Pupillary dilation was seen in 11 patients (26%). Thirty-six patients (85.5%) had automatisms; oroalimentary automatisms were observed in 21 (lip smacking in 12, chewing in five, and licking and tooth grinding in three and one, respectively), gestural automatisms in 10, and verbal automatisms in five. Positive motor signs were observed in 20 patients (47.6%); clonic version of the head was seen in eight patients, unilateral upper limb clonic seizures were observed in six patients, and unilateral dystonic posturing was seen in six patients. Two of the patients with positive motor signs had a prolonged focal seizures. Ictal aphasia was observed in four cases (9.5%). Two patients also had emeticus spectrum as clinical manifestation. Postictal manifestations, such as language deficits and cognitive impairment, were recognized in three (7%) and two (4.7%) patients, respectively. Seven patients (16.5%) had secondarily generalized seizures.

Seizure frequency was daily in 12 patients (28.5%), weekly in 19 patients (45.2%), monthly in eight patients (19%), and sporadic in three patients (7%). All patients had seizures while awake and five patients (12%) also had seizures during sleep.

3.6. EEG findings

3.6.1. Interictal EEG

We found a normal EEG in 20 cases (47.5%). Unilateral spikes or sharp waves were found in the anterior temporal area in 12 cases (29%), temporal rhythmic delta–theta activity was found in six

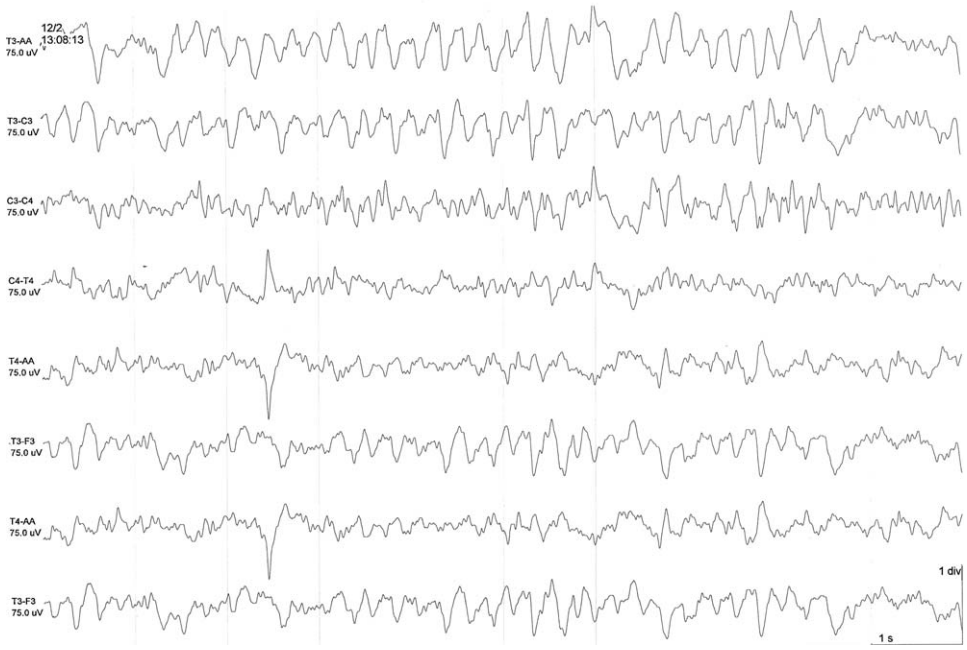

Fig. 1. Interictal EEG recording shows theta activity in left temporal lobe.

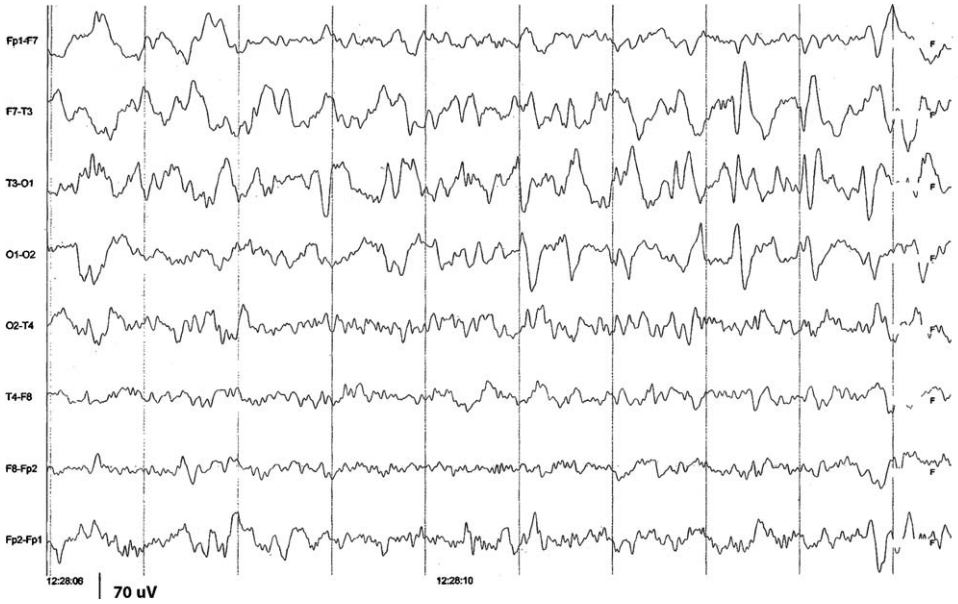

Fig. 2. Ictal EEG recording shows a rhythmic delta–theta activity followed by spikes in left temporal lobe.

cases (14%), and bilateral anterior spikes were found in four cases (9.5%) (Fig. 1).

3.6.2. Ictal EEG

The ictal EEG showed typical monomorphic rhythmic theta activity, progressively increasing in voltage in 30 patients (71.5%) and temporal flattening, followed by fast activity and finally by postictal slow waves, with temporal predominance in 12 patients (28.5%) (Figs. 2 and 3). A diffuse pattern was found in 10 patients (23%). The focal discharges were propagated to the ipsilateral hemisphere in six patients (14%) and to the contralateral hemisphere in three patients (7%). Two patients (4.5%) had an apparently generalized ictal pattern.

Multicontact electrodes carrying six platinum contacts were inserted orthogonally using high-resolution CT. Insertion of depth electrodes was done by standard stereotactic methodology using a Lexell frame. Depth-electrode recordings revealed right hypersynchronous hippocampal ictal discharges in two patients with bilateral hippocampal atrophy.

3.7. Neurologic examination and neuroradiological imaging

Physical examination was normal in all patients and in all of them abnormalities were found on the MRI (Fig. 4A and B). Thirty-nine patients (92.8%) had a unilateral signal of atrophy of the hippocampus (right in 21 and left in 18) and three patients (7.2%)

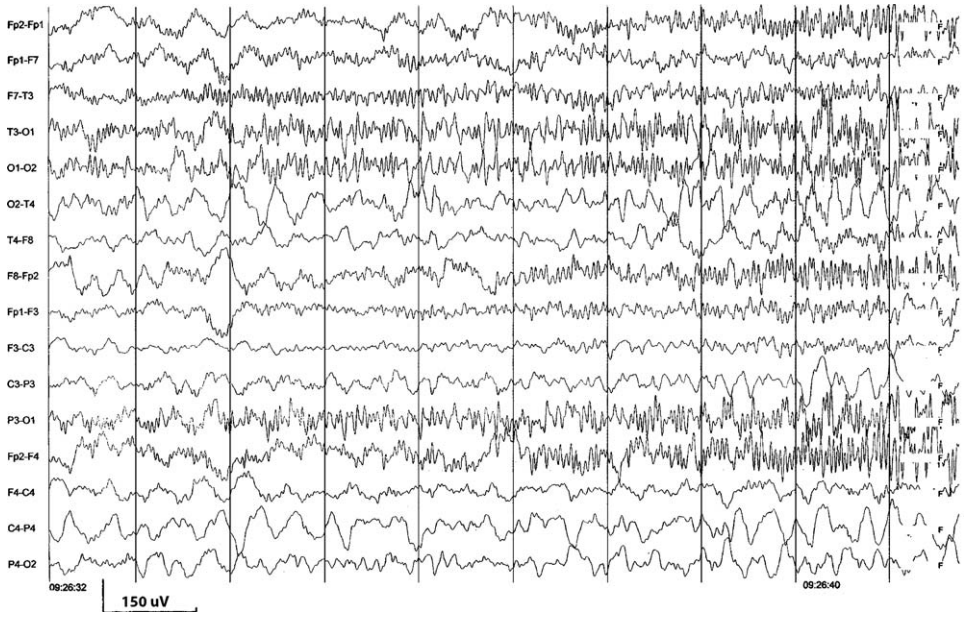

Fig. 3. Ictal EEG recording shows fast activity in left hemisphere propagated to right frontal area 30 s after seizure onset in left temporal lobe.

had bilateral hippocampal atrophy. Thirty-four patients (81%) had an increased signal on T2-weighted images and 37 patients (89%) had an increased signal on FLAIR.

Magnetic resonance spectroscopy demonstrated decreased *N*-acetylaspartate in all four cases studied.

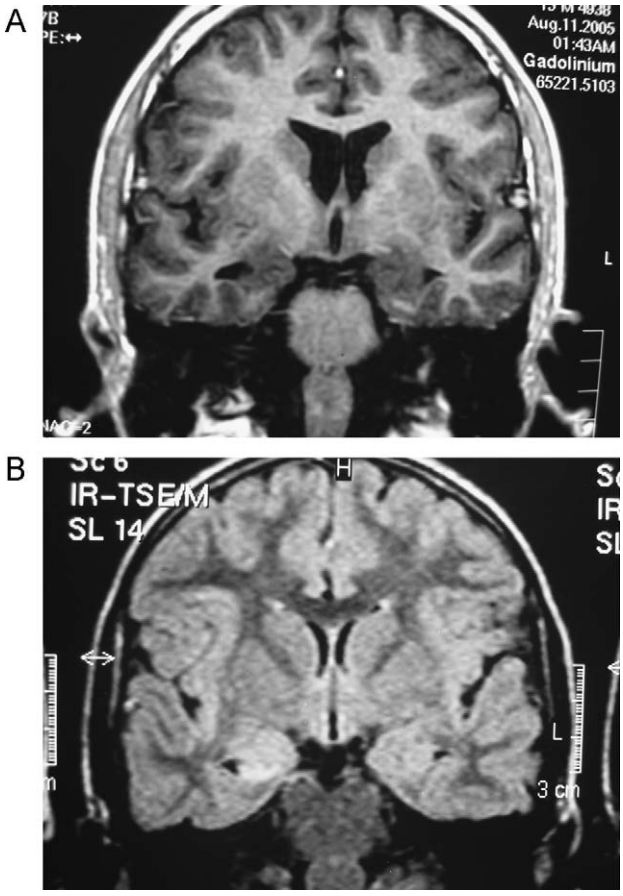

Fig. 4. (A) Coronal T1-weighted image showing right hippocampal atrophy. (B) Coronal T2, FLAIR image shows hyperintense signal in the right hippocampus

3.8. Neuropsychological assessment

Nineteen patients (45%) had behavioral disturbances, such as hyperactivity, impulsivity, and aggressive behavior. Twenty-four patients (57%) had learning difficulties.

The neuropsychological evaluation revealed a normal IQ in 27 patients (64%), a borderline IQ in nine patients (21.5%), and mild mental retardation in six patients (14%). Fifteen patients (35.5%) presented with a verbal memory deficit and 14 patients (33.5%) had a visual memory deficit.

Ten patients (23.5%) had a very bad quality of life, fifteen (36%) had a bad quality of life, thirteen (31%) a regular quality of life, and 4 (9.5%) a good quality of life.

3.9. Treatment

Thirty-eight patients underwent surgical treatment at a mean age of 13 years (range, 6–20 years) and after a mean duration of epilepsy of 5.5 years. Standard temporal lobectomy was performed in 32 patients (left side in 16 and right side in 16) as well. Selective amygdalohippocampectomy was performed in six patients (left side in three and right side in three). Four patients were treated with AEDs; two of them showed a good response and the other two turned out to be refractory to the AEDs. These latter two patients are currently undergoing pre-surgical evaluation.

3.10. Neuropathological findings

All of the 38 patients who underwent surgery had histopathological findings compatible with HS. These included neuronal loss in the CA1 region of the hippocampus with relative sparing of the CA2 region. Dysplastic cells were found in six patients.

3.11. Evolution

The mean post-surgical follow-up was 6.5 years (range, 3–9 years). Thirty-five patients are currently seizure free (Engel score class 1a) and three patients have an Engel score class 1b. Of the 38 patients who underwent surgery, 18 continue receiving AEDs, the number of AEDs was diminished in 12, and AEDs were withdrawn eight. In our present series of patients, the neuropsychological

profile has not changed post-operatively significantly; IQ increased and the quality of life improved.

Of the four cases who did not undergo surgery, two have refractory epilepsy and are being evaluated for surgery and the other two are responding well to AEDs without cognitive impairment and behavioral disturbances and have a good quality of life.

3.12. Electroclinical findings recognized according to age

According to the age, we divided our series of patients into three groups. The first group included nine patients that started with seizures before 2 years of age. Motor seizures were the most common clinical manifestation, characterized by clonic version of the head and unilateral upper limb clonic seizures. All patients in this group also presented with motor arrest and oroalimentary automatisms. Aura was difficult to recognize. In three of them, the interictal EEG recordings showed bilateral paroxysms predominantly in anterior regions, in addition to the focal abnormalities, and two had an apparently generalized ictal pattern. The second group included 17 patients that started with seizures between 2 and 10 years of age. In this group, patients also had oroalimentary manifestations, but the automatisms were more complex and the patients had less motor manifestations. The pattern was characterized by dystonic posturing and versive seizures. The interictal EEG recordings showed temporal abnormalities. The ictal EEG recordings showed lateralized abnormalities with a maximum in the temporal electrodes. The third group included 16 patients that started with seizures between 10 and 16 years of age. The most common clinical manifestation was abdominal aura followed by oroalimentary, gestural, and verbal automatisms. Dystonic posturing was also observed. The interictal and ictal EEG recordings showed well-localized abnormalities in the temporal lobes.

4. Discussion

Several series of pediatric patients with temporal lobe epilepsy including MTLE-HS have been published. The syndrome is not rare and may be identified adequately even in very young children.[8–21]

In our series of 42 patients suffering from MTLE-HS, we could identify three age groups. Nine (21.5%) children under the age of 2 predominantly had motor seizures, while 16 (38%) children over 10 years of age had the same clinical characteristics as adults. In between these years, 17 patients (40.5%) presented with seizures that tended to be relatively simple with progressive elaboration of automatisms as they grow older. Similar findings were reported by Ray and Kotagal.[17] However, Fontana et al.[19] found that in their group of very young children motor manifestations were less frequent. The difference of semiology of the seizures is strongly related to brain maturation and neuropsychological development. Aura is rarely observed in very young children, probably because they are not able to describe their subjective feelings and the clinical manifestation may be motor arrest accompanied by transient autonomic manifestations and simple oral automatisms with drooling. Accurate video-EEG recordings may demonstrate these types of seizure that often precede the motor manifestations. It is important to consider that MTLE-HS may start very early in life and that timely surgical intervention may avoid neuropsychological deterioration.

In our series of patients, 17 patients (44.4%) had had prolonged febrile seizures, and eight patients (19%) had had prolonged afebrile focal seizures. Whether hippocampal neuron loss precedes the seizure onset or is a result of repeated seizures, especially prolonged seizures, is an important question that has not been satisfactorily answered yet. Some evidence suggests that hippocampal neuron loss is an ongoing process, including following the development of seizures.[22,23] However, the relationship between a history of febrile seizures in early childhood, especially complex febrile seizures, and the development of the mesial temporal sclerosis in later life remains controversial, with contradictory evidence not only in favor, but also against this association.[24–27]

Mesial temporal lobe seizures associated with HS are generally indistinguishable from mesial temporal lobe seizures resulting from other types of mesial temporal lobe epilepsy and therefore do not characterize the syndrome itself, but are an important part of the clinical spectrum. Based on recent evidence, however, this concept may need to be changed as differences between the seizures of MTLE-HS and other types of mesial temporal lobe epilepsies have been reported.[19,28,29] Ipsilateral automatisms, contralateral dystonic posturing, and oral-alimentary automatisms may be characteristic of MTLE-HS, but not of mesial temporal lobe epilepsy resulting from neoplasms. However, further studies are necessary to better define the possible electroclinical differences between mesial temporal lobe epilepsies of different etiologies.

It is important to determine the seizures that may have lateralizing or localizing value. These seizures include lateralized motor manifestations, language signs, and postictal findings.[4] In MTLE-HS, head deviation, eye deviation or both, have lateralizing value, depending on when during the seizures such deviation takes place.[8,30] Early, relatively casual head deviation may be ipsilateral to seizure origin, but forced head and eye deviation occurring later in the seizures that evolve into generalized seizures, is almost always contralateral. Unilateral tonic or dystonic posturing is contralateral to the side of onset.[30,31] Ipsilateral automatisms occurring alone are not as consistent a lateralizing sign as dystonic posturing.[31] Contralateral ictal paresis has recently been reported as a reliable lateralizing sign. Ictal vomiting in MTLE-HS has been related to right temporal lobe onset, and unilateral eye blinking reportedly occurs on the same side as seizure origin.[4] Both ictal aphasia and ictal speech arrest have been considered with a seizure onset in the language-dominant temporal lobe, whereas verbalization of coherent speech is associated with seizure onset in the non-dominant temporal lobe.[32] All these potentially lateralizing signs are helpful during the presurgical evaluation of patients with medically refractory MTLE-HS. In Table 1, the lateralizing or localizing signs in MTLE-HS are listed.

Routine interictal EEG recordings were normal in approximately half of the patients. In three of nine of the very young children, the interictal EEG recordings showed bilateral abnormalities in addition to focal paroxysms. Ictal EEG recordings in two patients of this group had an apparently generalized ictal pattern. In childhood and adolescence, the interictal and ictal abnormalities are very similar to the EEG findings observed in the adult population.[4,5] Magnetoencephalography may localize interictal

Table 1
Lateralizing or localizing signs in MTLE-HS.

Motor manifestations
Head deviation, eye deviation, or both
Unilateral tonic or dystonic posturing
Contralateral ictal paresis
Language signs
Ictal aphasia
Ictal speech arrest
Verbalization of coherent speech
Postictal findings
Postictal aphasia
Deficit motor postictal
Others signs
Ictal vomiting
Unilateral eye blinking
Ictal automatisms with preserved consciousness (non-dominant hemisphere)
Nose wiping at the end of mesial temporal seizures (ipsilateral)

and ictal epileptiform discharges to mesial temporal structures in patients with mesial temporal lobe epilepsy.[33]

All our patients had abnormal MRIs with unilateral atrophy, increased signal intensity, and a normal contralateral hippocampus. In most of our patients, we found unilateral hippocampal atrophy and in three patients bilateral hippocampus atrophy was seen. We observed an increased signal on FLAIR (81%) and on T2-weighted images (82%) and in 14% mild neocortical changes were found. High-resolution MRI is useful to demonstrate hippocampal atrophy and MRI volumetry will demonstrate asymmetry. MRI is crucial for diagnosis, surgical treatment, and prognosis.[24,34–38] Magnetic resonance spectroscopy has demonstrated that hippocampal sclerosis is associated with a decrease in *N*-acetylaspartate,[39] as we observed in the four patients studied. F-fluorodeoxyglucose positron emission tomography is the most sensitive interictal imaging technique for identifying the focal functional deficit associated with temporal sclerosis.[40] Interictal SPECT is also capable of showing unilateral temporal hypoperfusion in MTLE-HS. Ictal SPECT may be useful to demonstrate unilateral temporal involvement.[41]

Formal neuropsychological testing is useful for demonstrating typical memory and learning disturbances in patients with MTLE-HS. It is also important to evaluate the cognitive evolution in the postoperative period.[2,4,5]

In the differential diagnosis, other types of focal epilepsies should be considered. Focal seizures of benign childhood epilepsy with centro-temporal spikes begin with sensory or motor phenomena around the mouth or upper limbs with typical functional spikes that are different from the complex focal seizures of mesial temporal origin. A variant of benign childhood epilepsy with centro-temporal spikes with affective symptomatology should also be considered as a differential.[42] In MTLE-HS, the early age at onset of the seizures, a history of complex febrile seizures and other early insults, increased incidence of seizures among family members, memory deficit, and hippocampal atrophy on MRI are features that distinguish this entity from other causes of mesial temporal lobe epilepsy. The same features are useful to distinguish patients with MTLE-HS from patients with complex focal seizures caused by lateral temporal or extratemporal lesions.[43]

The results of surgical treatment in our series of patients were excellent: 35 of 38 patients who underwent surgery are seizure free. The presurgical evaluation is usually performed noninvasively with video-EEG monitoring, MRI, and a neuropsychological evaluation. Some centers also use functional imaging with either PET or SPECT. In most of our operated patients, surgical resection was limited to the involved mesial temporal structures, the temporal pole, and only a small amount of lateral neocortex, resulting in no significant additional neurologic deficit, especially when the patient had memory disturbances previous to the surgery. If memory is intact, anteromesial temporal resection will result in a postoperative deficit, particularly when performed on the language-dominant side.[2,4,5,44] Patients with MTLE-HS may show different seizure onsets within the complex limbic network. However, to obtain good surgical results we should consider mesial temporal structures as a whole epileptogenic network in MTLE.[45]

Patients with MTLE-HS are generally refractory to medical treatment, have interictal behavior disturbances, and are thus excellent candidates for surgery. Presurgical evaluation may be accomplished noninvasively and a high percentage of patients becomes free of seizures postoperatively.[2,4,5] In patients with MTLE-HS that fail the trial of two or three appropriate AEDs at maximum tolerable doses, surgical intervention should be considered. Early surgical treatment may avoid irreversible psychosocial disturbances and a bad quality of life. The long-term postoperative prognosis is very good and it appears that children with MTLE-HS have a better surgical outcome compared to adults.[46] We may expect excellent postoperative seizure control when there is evidence of unilateral HS.

5. Conclusions

MTLE-HS represents a well-defined and distinct symptomatic epileptic syndrome, representing a subtype of mesial temporal lobe epilepsy.

In our series of pediatric patients with MTLE-HS, very young children had predominantly motor manifestations, sometimes associated with motor arrest, accompanied by transient autonomic manifestations and simple oral automatisms with drooling. Accurate video-EEG recordings are useful in demonstrating these type of seizures, that may also precede the motor manifestations. In childhood and especially in adolescence, the clinical manifestations are similar to the adult population.

MTLE-HS is easily diagnosed in most patients based on the characteristic presentation, seizure type, and diagnostic findings, which include increased incidence of febrile seizures and a family history of epilepsy, typical simple and complex focal limbic seizures, memory deficit, anterior temporal interictal EEG spikes, characteristic ictal-onset EEG pattern, and hippocampal atrophy on high-resolution MRI.

In our series of patients, surgical treatment was successful in most patients. Thus, early surgical intervention offers the greatest potential for restoring the patients to a normal life.

None of the authors has any conflict of interest to disclose. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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